9 | Amiodarone use and the risk of acute pancreatitis: Influence of different exposure definitions on risk estimation

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Background: The antiarrhythmic drug amiodarone has an extremely long half-life of approximately 60 days, yet this is hardly considered in observational studies of adverse effects of amiodarone, such as acute pancreatitis.

Objectives: To investigate the robustness of the association between amiodarone and the risk of acute pancreatitis against different exposure definitions.

Methods: All incident amiodarone users in the Dutch PHARMO database between 2005 and 2015 and two comparison groups were included: (1) incident users of a different type of antiarrhythmic drug and (2) age- and sex-matched subjects starting a non-antiarrhythmic drug. Different definitions were applied to amiodarone exposure, including dichotomized, continuous, and categorized cumulative definitions with lagged effects to account for the long half-life of amiodarone. For each exposure definition, Cox proportional hazards regression analysis was used to estimate the risk of acute pancreatitis associated with amiodarone use, while adjusting for confounding.

Results: This study included 15 378 starters of amiodarone, 21 394 starters of other antiarrhythmic drugs, and 61 579 starters of non-antiarrhythmic drugs. Compared with starters of other antiarrhythmic drugs, the adjusted hazard ratios (HRs) for the dichotomized definitions of exposure ranged between 1.21 and 1.43, for the continuous definitions of exposure between HR 1.13 and 1.22, and for the categorized cumulative definitions between HR 0.52 and 1.72. The HRs observed in the comparison with non-antiarrhythmic drugs users were generally higher: For the dichotomized exposure definitions, they ranged between 1.67 and 1.82, for the continuous exposure definitions between 1.39 and 1.70, and for the categorized cumulative exposure definitions between 0.68 and 2.55. Accounting for lagged effects had little impact on estimated HRs estimates.

Conclusions: This study demonstrates the the relative insensitivity to of the association between amiodarone and the risk of acute pancreatitis against a broad range of different exposure definitions. Accounting for lagged effects had little impact, possibly because treatment switching was uncommon in this population.

10 | Estimating cumulative risk in the presence of competing events and dependent censoring in pharmacoepidemiology studies

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Background: The occurrence of an outcome of interest may be unobserved due to competing events or censoring that is differential by exposure group. Studies have traditionally not addressed these problems.

Objectives: To demonstrate a straightforward approach for estimating cumulative risk of an outcome in the presence of competing events and dependent censoring.

Methods: We used a generalization of the risk function that is equivalent to a weighted Aalen-Johansen estimator to estimate the cumulative risk of an outcome prior to competing events, accounting for dependent censoring and confounding using inverse probability (IP) weights. We show an example using data from the Women's Interagency HIV Study (WIHS) and replicate a prior analysis (Lau, Cole, & Gange, 2009) of the association between patient history of injection drug use (IDU, exposure) and time to initiation of antiretroviral therapy (ART, outcome), with clinical disease progression (AIDS diagnosis or death) as a competing event.

Results: We estimated the 10-year cumulative risk of ART initiation among 1164 women who were HIV-positive, free of clinical AIDS, and enrolled at 6 clinical sites in the United States on December 6, 1995 (when the first protease inhibitor was approved by the FDA). Over 10 years of follow-up, 671 of the women initiated ART (57.6%). The prevalence of competing events prior to ART initiation was 30.6%; therefore, censoring participants experiencing competing events would inflate the estimate of ART initiation to 76.8%. Loss to follow-up was differential by exposure (13.9% unexposed vs 5.9% exposed). Using the cumulative incidence estimator that accounts for competing events, dependent censoring, and confounding, we found that 47.2% of patients with a history of IDU and 72.7% of patients without history of IDU initiated ART over 10 years prior to AIDS or death. The cumulative risk difference was −25.5% (95% CI: −33.1, −18.0) and corresponds to a hazard ratio of 0.56 (95% CI: 0.50, 0.62), consistent with previous work.

Conclusions: Ignoring competing events and dependent censoring can produce misleading estimates. Estimating the incidence of an outcome in the presence of competing events is straightforward using a cumulative incidence estimator and can easily incorporate IP weights for dependent censoring and confounding. Applying this estimator to the WIHS data, we found that initiation of ART was markedly lower among patients with a history of IDU.

11 | Diagnostics for informative censoring: Application to antipsychotic trials with high dropout rates

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Background: In clinical trials and observational studies, follow-up is often censored when patients are lost to follow up or when they switch treatment in a per-protocol analysis. Such censoring is informative of effectiveness/safety when patients leave a study or switch treatment for lack of efficacy/tolerability. This selection bias can be